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Applicant:	RAMPAL *et al.*	Examiner:	Micah Paul Young
Application No.:	09/941,970	Group Art Unit:	1615
Filing Date:	August 29, 2001		

Title: **Controlled Release Formulation of Erythromycin or a Derivative Thereof**

14/Reply for Recons
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2-19-03

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Christine Kenedy

Bet
3-4-03

Assistant Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO OFFICE ACTION DATED NOVEMBER 19, 2002

In view of the following remarks, reconsideration and allowance of this application are requested. Claims 1, 2, and 5-12 are pending with claims 1, 11, and 12 being independent.

Claim 1 is directed to a controlled release formulation of erythromycin A or a derivative thereof that is suitable for once daily administration. The formulation includes erythromycin from about 66% w/w to about 90% w/w of the total tablet weight and from about 0.1% to about 4% w/w of one or more pharmaceutically acceptable rate controlling polymers.

Claims 1, 2, 5-10, and 12 have been rejected as being obvious over Balkin (U.S. Patent No. 5,656,284) in view of Urquhart (U.S. Patent No. 4,851,232).

Balkin discloses a transmucosal tablet that includes a gel and a pharmaceutical. The preferred gels are produced from organic polymers that can be dissolved in aqueous solutions with mild heating and mixing, and as they cool they form strong gels at dilute

concentrations. The resulting gels have large pores for allowing movement of nonpolymer molecules within them. See col. 3, lines 61-67. Balkin states that suitable polymers to form the gels include are xantham gum, and locust bean gum. See col. 4, lines 5-10. Balkin also states that erythromycin is suitable for transmucosal administration using a buccal tablet. See col. 6, lines 43-48. Nonetheless, Balkin fails to describe or suggest a formulation suitable for once day administration, as recited in claim 1. Instead, Balkin describes a mucosal tablet that is suitable for delivering a therapeutically effective amount of a pharmaceutical:

> "placing the tablet in the mouth between the lip mucosa and gingival mucosa, and allowing it to remain there for a time sufficient to deliver a therapeutically effective amount of the pharmaceutical to the human."

See col. 4, lines 48-55. Balkin provides a single example of the use of the mucosal tablet, and thus infers to one of skill in the art the meaning of "a time sufficient time to deliver a therapeutically effective amount of a pharmaceutical." In Balkin's sole example, the patient is described as placing the tablet in his mouth for three hours per day, twice per day. See col. 10, lines 24-29. As such, one of skill in the art reading Balkin would not have modified his tablet to provide a formulation suitable for once daily administration.

There are additional reasons why it is unreasonable to conclude that Balkin is disclosing a formulation suitable for once daily administration, as described in claim 1. For example, Balkin describes the preferred maximum size of his tablet: "[t]he preferred maximum diameter of an elliptical, disc-like or round tablet can range from 0.2 cm to 2.0 cm and the thickness can vary from 0.1 cm to 1.0 cm[.]" See col. 8, lines 24-28. Thus, Balkin teaches a tablet that can have a diameter of 2.0 cm and a thickness of 1.0 cm -- and this table is intended to be placed in the mouth between the upper lip and the opposite upper gingival? Applicants respectfully submit that such a tablet is too large to be suitable for the extended placement necessary for once daily administration. For this additional reason, one of skill in the art reading Balkin would not have modified his tablet to provide a formulation suitable for once daily administration.

Urquhart discloses a drug delivery device that includes a body having a reservoir that expands and swells in the presence of fluid, which acts as a means of retaining the device in the stomach over an extended period of time. See col. 3, line 66 through col. 4,

line 14. The material forming the reservoir is a hydrophilic polymer, and "tiny pills" are present within the reservoir. See col. 4, lines 5-10 and 19-22. The pills include a core of a drug surrounded by a wall of a release rate controlling material that releases the drug in the stomach or, alternatively, prevents release in the stomach so that the release is in the intestine. See col. 4, lines 19-30. Urquhart discloses the hydrophilic polymeric materials as including sodium alginate, locust bean gum, and cellulose ethers such as hydroxypropylmethylcellulose. See col. 5, lines 1-13. Urquhart also discloses the use of erythromycin as a suitable drug to be delivered. See col. 6, lines 6-14.

Urquhart, however, does not describe or suggest a formulation that includes erythromycin from about 66% w/w to about 90% w/w of the total tablet weight and from about 0.1% to about 4% w/w of one or more pharmaceutically acceptable rate controlling polymers, as recited in claim 1. Urquhart's Example 4, which is directed to the pharmaceutical ingredients, mannitol and theophylline, is the only example that provides some numeric values for the components of the drug delivery device, and these values appear to be limited to the components that make up the "tiny pills." See col. 9, lines 26-45. As such, the few values provided for the components are insufficient to describe or suggest the percentages of either erythromycin or a rate controlling polymer. Thus, one of skill in the art reading Urquhart would have had no motivation, much less a direction to take, to modify Urquhart's delivery device to have the percentages of erythromycin and rate controlling polymers recited in claim 1.

The Office action states that "[o]ne of skill would have been motivated to combine the suggestions of Balkin and Urquhart because of the expandability and hydrophilicity of sodium alginate." Applicants respectfully disagree. First, there is no motivation to combine Balkin and Urquhart and, second, the differences between Balkin and Urquhart would have taught away from combining the teachings of these two patents.

For example, Balkin discloses buccal tablets and lists the numerous advantages of mucosal delivery using buccal tablets in comparison to oral tablets, including rapidity of action (col. 5, lines 36-53), ability to administer medications that cannot be administered orally (col. 5, line 54 through col. 6, line 7), reduction of the effect of a drug on non-drug related liver metabolism (col. 6, lines 12-32), attenuation of the affect of a first on the liver metabolism of a second drug (col. 6, lines 33-54), possible reduction of exposure of the liver to hepatotoxici drugs (col. 6, line 55 through col. 7, line 30), reduced exposure

of the gastrointestinal tract to the drug (col. 7, lines 31-47), ability to administer drugs that otherwise would interfere with the absorption of other drugs (col. 7, lines 48-53), ability to administer drugs that are adversely affected by the presence of food (col. 7, lines 54-60), and ability to reduce bloods lipids in ways not possible through oral administration (col. 7, line 61 through col. 8, line 4).

In describing these various advantages over oral delivery, Balkin effectively denigrates oral delivery. For example, Balkin explains how certain drugs, when administered orally, have deleterious side effects which are avoided when administered buccally. In particular, Balkin points to orally delivered estrogen as inducing liver production of clotting factors that can lead to phlebitis and pulmonary emboli. See col. 6, lines 18-25. Balkin also denigrates oral delivery because of the possibility of orally administered drugs affecting the liver metabolism of other drugs. Balkin describes problems with the oral administration of medications that inhibit metabolizing enzymes in the liver and medications that increases metabolizing enzymes in the liver. According to Balkin, by "administering both classes of these drugs using buccal tablet there would be less effect on the concentrations of other drugs and thus the avoidance of toxic as well as subtherapeutic drug levels." See col. 6, lines 35-43. Balkin particularly denigrates the use of oral delivery to deliver erythromycin, pointing to the side effects of such oral delivery, including "the destruction of normal GI flora resulting in diarrhea and overgrowth with dangerous organisms such as *C. difficile*." See col. 7, lines 31-36, 45, and 46. As such, Balkin clearly teaches away from delivering erythromycin in an oral tablet. Denigrating a concept clearly teaches away from that concept, and teaching away is clear evidence that there is no motivation to combine.

Urquhart discloses the need for a drug delivery system that stays in the stomach for a prolonged period to release the drug continuously at a controlled rate for absorption in the stomach or for passage into and absorption in the intestine. See col. 1, lines 37-43. According to Urquhart, the delivery system is advantageous because it should "eliminate the need for administering a number of single doses at periodic intervals. The convenience of using a drug delivery system, which releases the drug over a prolonged period of time as opposed to the administration of a number of doses, has long been recognized in the practice of medicine" See col. 1, lines 49-55. As described above, Balkin's tablet is used twice per day, i.e., administration of a number of doses. Thus,

Urquhart teaches away from the tablet disclosed by Balkin. As such, one of skill in the art reading both references would not have been motivated to combine the teachings because each reference teaches away from the other. For at least these reasons, claim 1 and dependent claims 2 and 5-10 are allowable.

Claim 12, like claim 1, recites a controlled release formulation of erythromycin A or a derivative thereof suitable for once daily administration in an amount from about 66% w/w to about 90% w/w of the total tablet weight with about 0.1% to about 4% w/w of one or more pharmaceutically acceptable rate controlling polymers. Accordingly, claim 12 is allowable over Balkin and Urquhart, taken separately or in combination, for the same reasons that claim 1 is allowable.

Claim 11 is directed to a monolithic controlled release formulation of clarithromycin comprising 1000 mg of clarithromycin. The total weight of the dosage unit is not more than 1500 mg.

Claim 11 has been rejected as being obvious over Al Razzak (U.S. Patent No. 6,010,718). Al Razzak discloses an extended release composition of an erythromycin derivative for the gastrointestinal environment. See Abstract. Al Razzak's composition consists of 500 mg of an erythromycin derivative, such as clarithromycin; a pharmaceutically acceptable polymer; and pharmaceutically acceptable excipients, fillers, extenders, and/or lubricants. See col. 3, line 56 through col. 4, line 26. Example 1 of the patent discloses three formulations of clarithromycin tablets, each containing 500 mg of clarithromycin, 100 – 300 mg of methocel, 160 – 360 mg monohydrate lactose, 30 mg talc, and 10 mg magnesium stearate. Each of the tablet formulations weights 1000 mg.

Al Razzak, however, does not describe or suggest a monolithic controlled release formulation of clarithromycin comprising 1000 mg of clarithromycin, as recited in claim 11. Instead, Al Razzak's sole description of tablets that contain clarithromycin discloses 500 mg of clarithromycin. For example, Al Razzak, discloses "[t]he daily dose of the composition of this invention administered to a host in single dose can be in the amounts from 500 mg to 1000 mg once-a-day[.]" See col. 5, lines 5-8. The term "500 mg to 1000 mg" is defined by Al Razzak as:

> "'500 mg or 1000 mg' as used herein, means the strength of tablet composition containing 500 mg clarithromycin, or the dose administered as 2x500 mg of clarithromycin respectively."

See col. 3, lines 8-12. In other words, a single dose of Al Razzak's formulation is either a single tablet to deliver 500 mg of active ingredient or two tablets to deliver 1000 mg of active ingredient. As such, it cannot be said that Al Razzak describes or suggests monolithic controlled release formulation of clarithromycin comprising 1000 mg of clarithromycin. Al Razzak's formulation instead contains 500 mg of clarithromycin. To provide 1000 mg of clarithromycin, Al Razzak teaches that two tables must be taken. Applicants submit that one of skill in the art reading Al Razzak would have found no teaching that would motivate one to double the amount of clarithromycin in the tablet.

The Office action states that the motivation would have been to optimize the dosage of the preparation following the teaching of Example 1. Applicants respectfully disagree. As described above, Example 1 of Al Razzak discloses three tablet formulations, each of which contains 500 mg of clarithromycin. The methocel and the lactose, however, are varied. As such, one of skill in the art reading Al Razzak, and in particular reading Example 1, would have been motivated to modify only the methocel and the lactose quantities, not the clarithromycin quantity. For these reasons, claim 11 is allowable over Al Razzak.

Authorization is given to charge any fees due in connection with this Response To Office Action to Deposit Account no. 50-0912.

Respectfully submitted,

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Date: February 19, 2003

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1615

TRANSMITTAL LETTER (General - Patent Pending)	Docket No. RLL-170US

In Re Application Of: **RAMPAL et al.**

Serial No.	Filing Date	Examiner	Group Art Unit
09/941,970	August 29, 2001	Michal Paul Young	1615

Title: **CONTROLLED RELEASE FORMULATION OF ERYTHROMYCIN OR A DERIVATIVE THEREOF**

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TO THE ASSISTANT COMMISSIONER FOR PATENTS:

Transmitted herewith is:

Response to Office Action mailed November 19, 2002
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in the above identified application.

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William D. Hare
Signature

Dated: **February 19, 2003**

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